A negative regulator of metastasis promoting macrophages

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Breast cancer is one of the leading causes of cancer death in women mainly because the breast cancer cells frequently egress from the primary site and form secondary tumors in the distant organs including the bone and lung (1,2). Since 5-year survival of patients is dramatically reduced once the metastatic tumors are established (2), it is necessary to understand the mechanisms behind the metastatic tumor expansion in order to improve the outcome of breast cancer patients.

It is now widely recognized that tumor infiltrating immune cells, especially tumor-associated macrophages (TAMs) promote the metastasis of solid tumors including breast cancer (3,4). Several mouse studies indicate that TAMs in the primary mammary tumors promote tumor angiogenesis, invasion, and intravasation, which promote tumor cell egress from the primary site (5-7). It is also reported that a distinct population of TAMs in the metastatic tumors, called metastasis-associated macrophages (MAMs), promote extravasation of circulating cancer cells as well as their survival and persistent growth in the metastatic site (8-11). Therefore, it has been suggested that targeting TAMs or MAMs can be a novel strategy to block the lethal metastasis formation and prolong the survival of patients with metastatic diseases (12).

It is well known that macrophages possess remarkable plasticity and can change their functions (e.g., promote or suppress the inflammatory responses) in response to factors in the microenvironment (13). Although TAMs in the primary tumors suppress immune reactions and promote tumor progression, several studies have suggested that activation of signaling pathways mediated by toll-like receptor (TLR), nuclear factor-κB (NFκB), or signal transducer and activator of transcription 3 (STAT3) can prompt TAMs to be pro-inflammatory and anti-tumor cells (14). Therefore, it is considered that changing the pro-metastatic phenotype of tumor-infiltrating macrophages is one of the attractive strategies to prevent macrophage-promoting metastasis formation, and signaling molecules that regulates MAM functions can be novel therapeutic targets for metastatic breast cancer.

In mouse models of breast cancer pulmonary metastasis, MAMs express a high level of vascular endothelial growth factor receptor 1 (VEGFR1) compared to resident alveolar macrophages (8), and macrophage-restricted deletion of VEGR1 suppresses pulmonary metastasis of breast cancer cells (15). The VEGFR1 inhibition in MAMs does not affect MAM accumulation in the metastatic lung but reduces their secretion of colony-stimulating factor 1 (CSF1) (15) that regulates phenotype of TAMs (16). These results thus suggest that VEGFR1-CSF1 autocrine signal is required for MAMs to maintain their pro-metastatic functions. However, signaling pathways or molecules that 'negatively' regulate pro-metastatic functions of MAMs are largely unknown.

A recent study published by Celus and colleagues in *Cell Report* (17) suggests that there is an intrinsic mechanism that suppresses metastasis promoting ability of MAMs. Using mouse models of spontaneous breast cancer metastasis, Celus *et al.* found that MAMs in the

metastatic lung expressed a high level of caveolin-1 (Cav1), an essential component of caveolae plasma membrane that mediates the internalization of cytokine receptors, and that genetic depletion of Cav1 significantly increased the number and size of lung metastatic foci. Since depletion of macrophages abrogated the increase in metastasis formation induced by Cav1 knockout, these results suggest that Cav1 expression in MAMs restricts their pro-metastatic functions. Mechanistically, Celus *et al*. have shown that Cav1 in MAMs internalizes surface VEGFR1 and reduces their secretion of CSF1 and matrix metallopeptidase 9 (MMP9), which reduces angiogenesis in the metastatic tumors. Interestingly, Celus *et al.* demonstrated that Cav1 expression was much less in TAMs in the primary tumors compare with that in MAMs and that Cav1 depletion did not affect the growth of primary tumors or metastatic tumors in the liver, suggesting that Cav1 mediated suppression in tumor promoting macrophage function is restricted to the lung microenvironment. This might be partly due to the abundant expression of CSF2 in the lung, since monocyte-derived macrophages cultured with CSF2 increased *Cav1* mRNA expression.

Although the requirement of the VEGFR1-CSF1 autocrine loop for pro-metastatic MAM function has been described previously (15), this work identified, for the first time, Cav1 as a negative regulator of VEGFR1 induced pro-metastatic features of MAMs. On the other hand, previous mouse studies indicate that MAMs in the metastatic lung express a high level of VEGFR1 and can promote metastatic tumor growth even in the Cav1 competent mice (8,15). Furthermore, in human breast cancer lymph node metastasis samples, a subset of MAMs express VEGFR1 and the number of VEGFR1 expressing stromal cells are significantly higher in the metastatic tumors than the primary tumors (15). It might be possible that Cav1 expression in MAMs is spatiotemporally regulated and is reduced in a minor population of MAM localized in a specific tumor area during the course of metastasis. Since VEGFR1 in MAM is required for metastatic tumor outgrowth (15), better understanding of Cav1 mediated VEGFR1 internalization in MAM subsets will lead to a novel strategy to improve outcome of metastatic breast cancer patients. However, the existence and biological and clinical relevance of CAV1 reduction in MAMs requires further analysis.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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